REMARKS

Applicants acknowledge receipt of a Final Office Action dated January 29, 2007 (hereinafter "the Office Action"). Reconsideration of the present application is respectfully requested in view of the foregoing amendments and the remarks which follow.

I Status of the Claims

Claims 1-17 and 19-99 are pending in the application, with claims 1, 17, 22, 23, 39, 60 and 82 being the independent claims. Claim 18 was previously canceled. Claim 49 is amended. The minor typographic amendment to claim 49 does not introduce new matter.

It is acknowledged that that amendment to claim 49 is submitted after final rejection of the claims. However, because the amendment does not introduce new matter, and either places the application in condition for allowance or at least in better condition for appeal, entry thereof by the Examiner is respectfully requested.

II. The Declaration Under 35 U.S.C. § 1.132

At page 4 of the Office Action, the PTO has rejected the Declaration filed August 7, 2006, as insufficient as being unsigned. Applicants provide herewith a properly executed Declaration.

III. Rejections Under 35 U.S.C. § 102

On page 3 of the Office Action, the PTO has rejected claims 1, 2, 4, 5, 10, 12, 39-41, 44, 48, 53, 54, and 70 under 35 U.S.C. § 102(e) as being allegedly anticipated by U.S. Publication 2003/0185869 to Wertz *et al.* (hereinafter "Wertz"). Applicants traverse. The rejection is overcome in view of the executed Declaration provided herewith.

IV. Rejections Under 35 U.S.C. § 103

On page 4 of the Office Action, the PTO has maintained the rejection of claims 1-11, 16, 17, 19-35, 39-54, 59-76, and 81 under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Publication 2002/0065256 to Karlsson *et al.* (hereinafter "Karlsson"). Applicants

traverse for reasons made of record in the previous Amendment and Reply, which are incorporated herein by reference.

With respect to independent claim 1, Karlsson does not teach or enable fluticasone particles having an effective average size of less than 900 nm. Karlsson only enables particles of 2000 nm, but does not enable smaller particles. *See* Karlsson Table 1. Karlsson *discloses* particles "less than" 1000 nm, but does not enable the person of ordinary skill in the art to prepare particles having an effective average particle size of less than about 900 nm, wherein "effective average particle size of less than about 900 nm" means that at least 50% of the particles of fluticasone or a salt thereof have a size of less than about 900 nm, as presently claimed.

Karlsson merely asserts (paragraph [0017]) that particles (including thaose are "produced by conventional techniques known per se. e.g. by micronization or by direct precipitation" and also states that "information about micronization can be found e.g. in 'The Theory and Practice of Industrial Pharmacy,' Lachman, Liebermann and Klang, 2nd Ed., 1976, Lea & Febiger, Philadelphia, USA." However, the techniques disclosed by Karlsson do not enable one to obtain the a population of particles in which at least 50% of the particles of fluticasone or a salt thereof have a size of less than about 900 nm, unlike the present invention, which *do* enable one to obtain the claimed population of particles. Moreoever, even *if* the Lachman textbook did disclose such information, Karlsson does not identify where in this reference such information may be found and, to the extent that Karlsson is essential material, is not properly incorporated by reference.

For at least these reasons, Karlsson does not fairly teach or enable all elements of claim 1 and the claims dependent thereon, and therefore cannot anticipate or render obvious these claims.

With respect to independent claim 17, the applicants particularly draw the Examiner's attention to the issue of sterile filtration. Claim 17 expressly requires "fluticasone particles sufficiently small to be sterile filtered." The present specification provides additional details at paragraph 0015: "very small fluticasone particles, *i.e.*, less than about 150 nm in diameter, are desirable as such compositions can be sterile filtered." It is therefore implicit that large particles of fluticasone are not suitable for sterile filtration. Given the general understanding of one of ordinary skill in that art knows that most bacterial and fungal contaminants are in

the 1000 nm range, it would not be possible to filter out such contaminants from a fluticasone formulation unless the particles were less than the size of the contaminants.

The Examiner asserts on page 5 of the Office Action that "¶ [0044] teach that a suspension containing the active agent and additional ingredients can be produced by sterile filtration." Applicants disagree. Karlsson is drawn to heat sterilization of glucocorticoid formulations as filtration methods were found to be unsatisfactory:

> We have also found that attempts at terminal sterilization of the pharmaceutical formulations, especially suspensions, e.g. aqueous suspensions, of glucocorticosteroids have all proved unsatisfactory. ***Such suspensions can not normally be sterilized by sterile filtration as most of the particles of glucocorticosteroid will be retained on the filter.***

Paragraph [0009]. (emphasis added) Paragraph 0044, cited by the Examiner specifically *excludes* filtration of formulations containing glucocorticoids (emphasis added):

> [0044] A sterile pharmaceutical formulation comprising a glucocorticosteroid, such as finely divided budesonide, rofleponide or rofleponide palmitate, sterilized according to the present process, can be prepared by mixing the sterilized glucocorticosteroid with any suitable additional ingredient, e.g. a surfactant, a pH regulating or chelating agent, an agent rendering the suspension isotonic or a thickening agent. ***All components, other than the glucocorticosteroid, can be produced by sterile filtration of their aqueous solutions.*** The resulting sterile suspension may be stored under an over pressure of a sterile and inert gas, e.g. nitrogen or argon, and should be filled under aseptic conditions into pre-sterilized containers to produce a sterile pharmaceutical product, e.g. using a blow/fill/seal system.

Karlsson therefore not only fails to teach the use of filter sterilization, but explicitly *teaches away* from it. Applicants therefore respectfully believe that the rejection under 35 U.S.C. § 103 has been overcome and request reconsideration and withdrawal of the rejection.

V. Rejections Under 35 U.S.C. § 112, First Paragraph

At pages 6-7 of the Office Action, the Examiner has rejected previously presented claims 82-99 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. The Examiner states:

> These claims are directed towards a composition comprising solid particles of an agent coated with one or more surface modifiers. The specification does not disclose coating solid particles of an immunosuppressive agent with a surface modifier. There is no disclosure of coating any type of particles in the specification. This is considered new matter and thus rejected.

Id. Applicants traverse. As an initial matter, Applicants note that a table which listed exemplary support for claims 82-99 was provided at pages 25-26 of the Amendment of November 3, 2006.

As to the specific assertions of the Examiner, Applicants do not agree that "the specification does not disclose coating solid particles of an immunosuppressive agent with a surface modifier. There is no disclosure of coating any type of particles in the specification," as is alleged. The present application is drawn to fluticasone compositions. Fluticasone, like the other corticosteroids, achieves its therapeutic effects through immunosuppression. Not only is this well known in the art, but the specification describes the various use of fluticasone for allergic disease, asthma, and other allergic diseases. Moreover, US 2005/0244503, from which claims 82-99 were copied, states at paragraph 0107:

> [0107] Specific immunosuppressants include . . . corticosteroids (e.g., prednisolone, methylprednisolone, cortisone, fluticasone, beclomethasone, hydrocortisone). . .

Accordingly, by recitation of fluticasone, the present application provides support for "an immunosuppressive agent."

As to the allegation that the specification does not disclose coating solid particles, Applicants direct the Examiner to the specification, which recites, for example:

> Nanoparticulate compositions, first described in U.S. Patent No. 5,145,684 ("the '684 patent"), are particles comprising a poorly soluble therapeutic or diagnostic agent having associated with the surface thereof a non-crosslinked surface stabilizer.

> The '684 patent does not describe nanoparticulate compositions of fluticasone.

Paragraph [0003], page 1.

> [0024] The present invention relates to compositions comprising fluticasone and at least one surface stabilizer.

Paragraph 0024, page 10.

> [0090] The invention provides compositions comprising fluticasone particles and at least one surface stabilizer. The surface stabilizers adsorb to or associate with the surface of the fluticasone particles. Surface stabilizers useful herein do not chemically react with the fluticasone particles or itself. Individually adsorbed molecules of the surface stabilizer are essentially free of intermolecular cross-linkages. The compositions can comprise two or more surface stabilizers.

Paragraph 0090, page 28.

> Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

Paragraph 0129, page 37. It is therefore clear to the person of ordinary skill in the art that the surface modifiers are coated onto the surface of the fluticasone particles. Applicants therefore respectfully believe that they have overcome the Examiner's rejection and request its reconsideration and withdrawal.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that all of the pending claims are now in condition for allowance. An early notice to this effect is earnestly solicited. If there are any questions regarding the application, the Examiner is invited to contact the undersigned at the number below.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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